Remarks/Arguments

Claims 33 and 50 have been amended, and claim 55 has been canceled. Claims 33, 44-54 and 56-58 remain in the application.

The Objection to the Specification

The Examiner objected to the specification because it contains an embedded hyperlink at page 21, line 11. By way of the foregoing amendment to the specification, the hyperlink has been deleted.

The Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 33 and 44-58 under 35 U.S.C. § 112, first paragraph for failure to comply with the enablement requirement. Specifically, the Examiner has stated that the specification does not enable one skilled in the art to which it pertains to make or use the invention commensurate with the scope of the claims.

The first paragraph of Section 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A 1971). A specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*, 858 F.2d at 737. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Id.* The *Wands* court set forth a number of non-exclusive factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows:

(1) the quantity of experimentation necessary,

(2) the amount of direction or guidance presented,

(3) the presence or absence of working examples,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the relative skill of those in the art,

(7) the predictability or unpredictability of the art, and

(8) the breadth of the claims.

Id.

Breadth of the Claims

With respect to the breadth of the claims, the Examiner finds that the specification teaches that tenascin-C is expressed in a variety of non-diseased tissues. In support of this statement, the Examiner refers to Figure 7 of the instant specification and states that this figure illustrates tenascin-C expression in liver, lung, spleen, intestine, and kidney. The Examiner further finds that the specification teaches only the detection of three specific xenografted tumor cell lines in mice with a single tenascin-C nucleic acid ligand, whereas the claims are broadly drawn to detecting cancer. In light of these teachings, the Examiner finds that the claims are unduly broad.

Applicant first notes that courts have determined that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970).

The Applicants respectfully disagree with the assertion that the specification teaches the expression of tenascin-C in non-diseased tissues. At that the time of filing the application, it was well known in the art that tenascin-C is expressed during embryogenesis. In adults, it expressed during wound healing, neoplasia, hyperproliferative skin disorders (such as psoriasis) and in atherosclerosis. See page 1, lines 17-32 where there is an extensive discussion of the prior art teaching that tenascin-C is expressed exclusively in such diseased tissue. In the case of tumors, tenascin-C expression is predictive of local tumor recurrence and is correlated with invasiveness and distant metastasis. See for example, Jahkola et al., *Eur. J. Cancer* 34:1687-1692 (1998);

Ishihara et al., *Clin. Cancer Res.* 1:1035-1041 (1995); Jahkola et al., *Br. J. Cancer* 78:1507-1513 (1998).

Figure 7, contrary to the Examiner's assertion, does not teach otherwise. Figure 7 illustrates the biodistribution of ^{111}In-DOTA or ^{111}In-DTPA radiolabeled tenascin-C aptamer. DOTA and DPTA are the chelators used to conjugate the ^{111}In radiolabel to the aptamer. It can be seen in Figure 7 that ^{111}In label is observed in liver, spleen, and kidney. It was well known in the art at the time the instant application was filed that the chelating agent used in the preparation of radiopharmaceuticals can effect the biodistribution of the radiopharmaceutical in a living animal. For example, different chelators can cause the non-specific uptake of radiopharmaceuticals to the kidneys, intestine, hepatobiliary system and lungs, even when the radiopharmaceutical comprises a specific targeting agent--such as a monoclonal antibody or aptamer--that would not be expected to bind in those regions. Such distributions are well known in the art as the inevitable consequence of administering an agent to living, metabolizing organism with a circulatory system. One skilled in the art realizes that after waiting an appropriate period to allow this normal tissue clearance of radioactivity to occur, the patient may then be imaged, and tumors are identified by defining regions of the body with increased tracer uptake See, for example, Bast et al., *Cancer Medicine*, 5th Edition, § 16, Part 65 (2000) (available online at << http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Books>>) where the authors state:

> In radioimmunoscintography, a tumor-specific antibody is labeled with a radionuclide that can be visualized outside the body by nuclear medicine imaging methods. After waiting an appropriate period for normal tissue clearance of radioactivity to occur, the patient is imaged, and tumors are identified by defining regions of the body with increased tracer uptake. ...

See also Hjelstuen, *Analyst.* 120: 863-866 (1995) . Indeed, the instant specification teaches at page 23, lines 29-32:

> Tc-99m radioactivity also appears in other tissues, notably the small and large intestines. The hepatobiliary clearance pattern seen here can be readily altered by one skilled in the art, for example by altering the hydrophilicity of the Tc-99m chelator,

> changing the chelator, or changing the radiometal/chelator pair together.

Similarly, at page 25, lines 23-29 (referring to Figure 7):

> This experiment indicates that the chemical properties of the chelator have a large effect on the distribution of the radiolabel of TTA1/GS7641 within a living animal. Biodistribution patterns that are different from Hi15-TTA1/GS7641 may be useful for targeting tumors under certain conditions where hepatobiliary clearance is undesired. Such conditions include, but are not limited to radiotherapy applications as well as imaging of the intestines, prostate and other abdominal regions.

Thus, one skilled in the art at the time the application was filed would appreciate that the presence of the radiolabel in the normal tissues mentioned by the examiner does not indicate that those tissues express tenascin-C. Moreover, one skilled in the art, guided both by the prior art at the time of filing and the specific teachings of the instant specification quoted above, would be able to discriminate between tumor specific expression of tenascin-C and the non-specific presence of the label in certain tissues as a result of hepatobiliary clearance. For example, see Figure 3 of the instant specification where tumors are clearly visible despite the additional radioactivity in the gastrointestinal tract. Finally, the specification teaches that one may alter a hepatobiliary clearance pattern by altering the hydrophilicity of the chelator, changing the chelator, or changing the radiometal/chelator pair together. For example, the specification teaches that if one wants to perform abdominal imaging, then one selects a chelator that has a relatively low level of hepatobiliary clearance. See page 25, lines 23-39.

Turning now to the Examiner's finding that the specification teaches only detection of a few types of cancer using a single tenascin-C nucleic acid ligand whereas the claims are drawn broadly to the detection of cancer, Applicant respectfully submits that there is a reasonable correlation between the scope of the claims and the enabling disclosure of the specification. Applicants have provided examples of the detection of widely varied types of human tumors xenografted into mice including (with reference to the cell types listed in Figure 6):

neural tumors	U87 glioblastoma-astrocytoma U251 glioma
breast tumors	MDA-MB-468 poorly metastatic breast cancer MDA-MB-435 highly metastatic breast cancer
colorectal tumors	SW620 colonic carcinoma
soft tissue sarcoma	A673 rhabdomyosarcoma

The prior art is replete with descriptions of the utility of the mouse xenograft model in the development of methods for the detection and treatment of human tumors, indicating that the mouse xenograft model is recognized in the art as an *in vivo* model that correlates well with human tumors. For example, see Rofstad & Lyng, *Mol Med Today.* 2:394-403 (1996) (xenograft model systems for human melanoma); Clarke, *Breast Cancer Res Treat.* 39:69-86 (1996) (xenograft model systems for breast cancer); Thompson et al., *Biochim Biophys Acta.* 1400(1-3):301-19 (1998) (describing success of mouse xenograft model system in developing cancer therapeutics). In Bast et al., *Cancer Medicine*, 5th Edition, § 13, Part 42 (2000), the authors state:

> The success of human tumor xenografting into the nude mice and the ability to maintain the histologic and biologic identity of tumors through successive passages in vivo revolutionized many aspects of cancer research, including drug development. Transplantation of tumor cell lines into nude mice can be accomplished via multiple routes: subcutaneous, intraperitoneal, intravenous, intracranial, intrasplenic, renal subcapsular, or through a new orthotopic model by site-specific organ inoculation. Each site has specific advantages and limitations.
> ....
> Despite these changes in kinetics of invasive potential, the majority of the xenografted human tumors maintain the morphologic and biochemical characteristics of their original tumors. Therefore, it is expected that chemosensitivity would be similar in both the original and the xenografted human tumor, and that this correlation would predict for both active single agents and active drug combinations. In fact, excellent correlations can be made between average growth delay for human tumors in nude mice treated with the best available drug combinations and complete clinical response rates. ...

With respect to tenascin-C specifically, there are numerous reports of the use of the xenograft tumor model in combination with radiolabeled monoclonal antibodies. For example, Bourdon et al., *Anticancer Res.* 4(3):133-40 (1984) describe the use of the anti-

tenascin antibody 81C6 to image human tumor xenografts in mice. Indicating that such studies of the 81C6 antibody correlate well with studies in humans, Schold et al., *Invest Radiol.* 28(6):488-96 (1993) and Zalutsky et al., *Cancer Res.* 15;49(10):2807-13 (1989) describe the use of radiolabeled 81C6 to image tumors in human patients; and Reardon et al., *J Clin Oncol.* 20(5):1389-97 (2002) describe the use of 81C6 to treat human tumors.

The prior art includes the descriptions of many types of tumors that express tenascin-C (including carcinomas of the lung, breast, prostate, colon, astrocytomas, glioblastomas, melanomas, and sarcomas), as well as other diseases such as hypoproliferative skin disorders (e.g., psoriasis). See page 1, line 17- page 2, line 1 of the instant specification where such descriptions are incorporated by reference. At the time the instant application was filed, tenascin-C had additionally been implicated in numerous other neoplasms, including: basal cell carcinoma (Stamp, *J Pathol.* 1989 Nov;159(3):225-9), odontogenic tumors (Heikinheimo et al., *Virchows Arch B Cell Pathol Incl Mol Pathol.* 1991;61(2):101-9), endometrial adenocarcinoma (Vollmer et al., *Lab Invest.* 1990 Jun;62(6):725-30), hepatocellular carcinoma (Yamada et al., *Liver.* 1992 Feb;12(1):10-6), salivary gland tumors (Soini et al., *Virchows Arch A Pathol Anat Histopathol.* 1992;421(3):217-22), transitional cell carcinomas of the bladder (Tiitta et al., *Virchows Arch B Cell Pathol Incl Mol Pathol.* 1993;63(5):283-7), and in rhabdomyosarcomas, fibromas and liposarcomas (Schnyder et al., *Int J Cancer.* 1997 Jul 17;72(2):217-24).

In summary, the prior art recognizes that tenascin-C is expressed in a tremendous variety of human tumors, and in hyperproliferative skin disorders and atherosclerosis. As explained above, Figure 7 in the instant specification does not demonstrate extensive expression in normal tissue. The prior art also recognizes the general utility of the mouse xenograft model for the study of human tumors. Finally, the prior art recognizes that the specific utility of the mouse xenograft model for the study of human tumors expressing tenascin-C. Thus, Applicants submit that by providing actual reduction to practice of the detection of xenografted human tumors of widely diverse origins, the scope of enablement reasonably correlates with the scope of the claims.

Nature of the Invention

The Examiner submits that the nature of the invention is such that detecting a disease using a ligand would require a teaching of a relationship between the ligand and the disease wherein the teaching would include an illustration or examples of the relationship between the ligand and the disease. As an example, the Examiner suggests a sample population study illustrating that tenascin-C expression detects cancer regardless of the amount, time, or pattern of expression.

As detailed in the foregoing section of this office action response, the state of the art at the time of filing of the invention was such that it was known that tenascin-C is expressed during embryogenesis, and during certain disease processes in adults, including cancer, proliferative skin disorders and atherosclerosis. See page 1, lines 17-32 of the instant specification where there is discussion of the types of diseased tissue where tenascin-C is expressed. The prior art also teaches that radiolabeled antibodies that bind tenascin-C are used for imaging and therapy of tumors in a clinical setting. See page 1, line 33-page 2 line 1. In addition, the specification provides examples in which tenascin-C aptamer recognizes a variety of morphologically distinct human tumors that have been xenografted into mice. Thus, the specification provides a teaching of the clear relationship between tenascin-C expression and disease.

As also explained in the foregoing section of this office action response, Figure 7 of the application does not depict the expression of tenascin-C in non-diseased tissues. Rather, Figure 7 depicts the inevitable hepatobiliary clearance pattern of a radiopharmaceutical in a living animal. Such hepatobiliary clearance patterns are well known in the radiopharmaceutical art. The specification teaches that one may alter a hepatobiliary clearance pattern by altering the hydrophilicity of the chelator, changing the chelator, or changing the radiometal/chelator pair together. See page 23, lines 29-32 . For example, the specification teaches that if one wants to perform abdominal imaging, then one selects a chelator that has a relatively low level of hepatobiliary clearance. See page 25, lines 23-39.

For the foregoing reasons, Applicant respectfully submits there is a clear teaching of the relationship between tenascin-C expression and the diseases of cancer, psoriasis

and atherosclerosis which would enable one skilled in the art to make and use the invention as claimed.

Level of Predictability in the Art

The Examiner states that the level of predictability in the art is very low with regard to detection of disease without a correlating relationship between the disease and the detecting molecule. The Examiner also states that the relationship between tenascin-C expression and cancer, psoriasis or atherosclerosis is unknown and that Figure 7 of the specification illustrates the expression of tenascin-C in normal tissue.

As discussed in detail above, the prior art clearly teaches a correlating relationship between expression of tenascin-C and cancer, psoriasis and atherosclerosis. See page 1, lines 17-32 of the specification. The prior art also teaches that radiolabeled antibodies that bind tenascin-C are used for imaging and therapy of tumors in a clinical setting. See page 1, line 33-page 2 line 1. Thus, the specification provides a teaching of the clear relationship between tenascin-C expression and disease.

In addition, Figure 7 of the application does not depict the expression of tenascin-C in non-diseased tissues. Rather, Figure 7 depicts the inevitable hepatobiliary clearance pattern of a radiopharmaceutical in a living animal. Such hepatobiliary clearance patterns are well known in the radiopharmaceutical art. The specification teaches that one may alter a hepatobiliary clearance pattern by altering the hydrophilicity of the chelator, changing the chelator, or changing the radiometal/chelator pair together. See page 23, lines 29-32 . For example, the specification teaches that if one wants to perform abdominal imaging, then one selects a chelator that has a relatively low level of hepatobiliary clearance. See page 25, lines 23-39.

For these reasons, one skilled in the art would readily extrapolate the prior art teachings--that tenascin-C expression correlates with disease and that tenascin-C antibodies may be used for therapy and detection of those diseases--to the claimed invention. MPEP § 2164.03. Therefore, contrary to the Examiner's assertion the level of predictability in the art is high with regard to detecting tenascin-C in order to detect a disease.

Existence of Working Examples

The Examiner asserts that the specification does not provide working examples of the broadly claimed invention, stating that the specification teaches the expression of tenascin-C in a variety of non-diseased tissues. Applicants respectfully disagree.

It has been determined by the courts that no working examples are required to enable a patent application. *In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642 (C.C.P.A. 1970). Applicant, however, has provided a number of specific *in vivo* examples of the detection of widely varying types of human tumors using the art-recognized mouse xenograft model. The state of the art is such that the mouse xenograft model for tumor detection is accepted as reasonably correlating with the detection of human tumors *in vivo*. Note that a rigorous or invariable exact correlation is not required. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985). As discussed above in detail, the prior art recognizes both the general utility of the mouse xenograft model for the study of human tumors and the *specific* utility of the mouse xenograft model for the study of human tumors expressing tenascin-C. For example, Bourdon et al., *Anticancer Res.* 4(3):133-40 (1984) describe the use of the anti-tenascin antibody 81C6 to image human tumor xenografts in mice. Indicating that such studies of the 81C6 antibody correlate well with studies in humans, Schold et al., *Invest Radiol.* 28(6):488-96 (1993) and Zalutsky et al., *Cancer Res.* 15;49(10):2807-13 (1989) describe the use of radiolabeled 81C6 to image tumors in human patients; and Reardon et al., *J Clin Oncol.* 20(5):1389-97 (2002) describe the use of 81C6 to treat human tumors.

Contrary to the Examiner's assertion, Figure 7 of the application does not depict the expression of tenascin-C in non-diseased tissues. Rather, Figure 7 depicts the inevitable hepatobiliary clearance pattern of a radiopharmaceutical in a living animal. Such hepatobiliary clearance patterns are well known in the radiopharmaceutical art. The specification teaches that one may alter a hepatobiliary clearance pattern by altering the hydrophilicity of the chelator, changing the chelator, or changing the radiometal/chelator pair together. See page 23, lines 29-32 . For example, the specification teaches that if

one wants to perform abdominal imaging, then one selects a chelator that has a relatively low level of hepatobiliary clearance. See page 25, lines 23-39.

In summary, the specification provides examples of the detection of widely varied human tumors using the art-recognized mouse xenograft model. Applicant submits that the Examiner's focus on the difference between the working examples and the claimed methods is based on a standard of a rigorous or exact correlation, which is not the standard of enablement. The prior art recognizes that tenascin-C is an important marker for the detection of diseased tissue, including cancer, psoriasis and atherosclerosis (see page 1, lines 17-33 of the instant specification). Figure 7 of the application is not to the contrary. The prior art also recognizes that detection of tenascin-C in human tumors in xenografted mice correlates with the detection of tenascin-C expression in tumors in humans. For these reasons, Applicants respectfully submit that the specification provides working examples of the claimed invention which would enable one skilled in the art to make and use the invention as claimed.

Quantity of Experimentation Required

The Examiner submits that it would require undue experimentation for one skilled in the art to make and use the invention as claimed in view of the breadth of the claims, the nature of the invention, the unpredictability in the art, and the lack of working examples. Applicants respectfully disagree. As detailed in the foregoing sections of the response, Applicants have demonstrated that the art recognizes the correlation between tenascin-C expression and cancer, psoriasis and atherosclerosis. The Applicants have also demonstrated that the art recognizes the correlation between the detection and treatment of human tumors xenografted into mice with the detection and treatment of humans with the same tumors. In the specific case of tumors that express tenascin-C, the Applicants have demonstrated that the art recognizes the correlation between the detection of tenascin-C expression in xenografted mice and the detection and therapy of the same tumors in humans. Applicants have demonstrated that a representative tenascin-C nucleic acid ligand detects a wide variety of human tumors in xenografted mice.

While development of a specific treatment or detection regimen may require a large quantity of experimentation, the amount of experimentation is not a controlling factor. It

is a tenet of patent law that an applicant need not teach what the skilled artisan already knows. Instead, it is preferred that an applicant "omit what is known in the art." *Hybritech Inc. v. Monoclonal Antibodies*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). Certainly, much guidance and direction exists in the prior art with regard to administration routes and other details of treatment regimens. Antisense and other nucleic acid therapeutics have been used in the treatment of humans since at least as early as 1993. Additionally, the specification provides extensive teaching of the preparation, administration, and analysis of treatment data in *in vivo* experiments. Applicants submit that such prior art treatments, together with the teachings of the specification, provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed and, and therefore satisfy the enablement requirement. Reconsideration is respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 33 and 44-58 under 35 U.S.C. § 112, Second Paragraph as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claim 33, the Examiner states that the claim does not include a step for disease detection. Claim 33 has now been amended to recite a disease detection step.

With regard to claim 50, the Examiner states that it is unclear as to whether the sequences of Tables 3, 4, and Figure 2 are the same or different from SEQ ID NO: 4-65. Applicant notes first that the sequences in Tables 3, 4, and Figure 2 are the same as SEQ ID NO: 4-65. Applicant has amended claim 50 to recite only SEQ ID NO: 4-65.

Claim 55 has been canceled without prejudice. Withdrawal of the 35 U.S.C. § 112, Second Paragraph rejection of claim 54 is respectfully requested.

The 35 U.S.C. § 102 Rejection

The Examiner has rejected claims 33, 44-55, and 57-58 under 35 USC § 102(a) as being anticipated by Hicke et al. (J.Nuc. Med. May 1999, 40(5):99) as defined by Hicke (slide presented by Brian Hicke at the Society of Nuclear Medicine Meeting held in Los Angeles, CA on June 7-10, 1999).

Applicants have submitted a declaration by inventors Brian Hicke and Stephen Warren under 37 C.F.R. § 1.132. The inventors declare that both the J. Nuc. Med. abstract and the slide displayed at the Society of Nuclear Medicine Meeting are publications of their own work. Hence, the reference invention is not "by another" and is not therefore a prior art disclosure of the claimed invention under 35 U.S.C. § 102(a).

Furthermore, the slide presented at the Society of Nuclear Medicine Meeting, June 7-10, 1999 does not depict the TTA1 ligand as claimed in claims 50-55. Specifically, comparison of the slide and of the TTA1 sequence in claims 50-55 reveals there are a number of nucleotide differences. First, nucleotide position 10 in the slide is "A" and nucleotide position 11 in the slide is "U" (nucleotides 10 and 11 in the slide are depicted as forming a base pair wherein the nucleotides are separated from one another in the linear sequence by $(CH_2CH_2O)_6$). In the true TTA1 sequence as claimed in claims 50-54, nucleotide position 10 is "C" and nucleotide position 11 is "G." Nucleotides 9 and 10 in the true TTA1 sequence form a G-C based pair in which the nucleotides are separated from one another in the linear sequence by $(CH_2CH_2O)_6$. In other words, the slide depicts an extra A-U basepair relative to the true TTA1 sequence.

Second, the slide displays additional differences from the true TTA1 as claimed in claims 50-55. Specifically, the slide indicates in emphasized type that certain G residues are 2'OH, including the G residues at position 1, 13, 16, and 19. At the time the slide was displayed, the speaker (Brian Hicke) stated that the non-emphasized G residues are 2'OMe (see the 37 C.F.R. § 1.132 declaration of Brian Hicke). It can be seen that the G residue at position 9 is a 2'OH G in the TTA1 sequence as claimed, but is shown as a 2'OMe G in the slide.

Thus, there are a number of differences between the TTA1 sequence claimed in claims 50-54 and the slide which purports to depict TTA1. Applicants respectfully submit that the true TTA1 sequence as claimed in claims 50-54 is not anticipated by the distinct sequence presented in the slide.

In light of the fact that the prior art cited by the Examiner is the inventors' own publication, and further in light of the fact that the TTA1 sequence claimed in the instant application is not the same as the purported TTA1 sequence presented in the inventors' slide, Applicant respectfully requests that the 35 U.S.C. § 102(a) rejection be withdrawn.

Conclusion

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date: June 1, 2004

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